

Applicants: David M. Stern et al.
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In the Specification

Please delete the entire section of the specification entitled "Brief Description of the Figures", beginning on page 4 and ending on page 6.

Please replace the paragraph beginning on page 31, line 27, with the following paragraph:

RAGE-dependent binding to brain microvessels ~~(Fig. 1a)~~ and transport across the BBB ~~(Fig. 1b)~~ of human and mouse A β ₁₋₄₀, and somewhat slower, but significant RAGE-dependent BBB transport of A β ₁₋₄₂ ~~(Fig. 1b)~~ and absence of its significant binding to microvessels ~~(Fig. 1a)~~ were found in mice ~~(shown in Fig. 1a)~~ and guinea pigs. A β transport into brain was significantly inhibited by 65% to 85% by circulating α -RAGE IgC (5-40 μ g/kg) and abolished sRAGE. Several other molecular reagents including fucoidan (a ligand for the scavenger receptor type A), anti- β 1-intergrin antibodies, or RHDS peptide (5-9 sequence of A β) did not affect either BBB transport or binding of A β ~~(Figs. 1a and b)~~. Although A β peptides were partially metabolized during their transport across the BBB (i.e., \leq 50% for 10 min), significant and rapid RAGE-dependent neuronal uptake of circulating A β was observed after the BBB transport ~~(Fig. 1e)~~.

Please replace the paragraph beginning on page 32, line 14, with the following paragraph:

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Transport of $A\beta_{1-40}$ across the BBB was associated with an early cellular stress response that preceded changes in the CBF. The expression of TNF- α mRNA and protein on different cells in brain parenchyma, including neurons and brain endothelium was evident after 15 min of transport of circulating $A\beta$ across the BBB (~~Fig. 2a~~). Treatment with circulating sRAGE (~~Fig. 2a~~) or α -RAGE IgC abolished $A\beta$ -induced TNF- α expression. $A\beta$ transport across the BBB resulted in rapid neuronal expression of IL-6 (~~Fig. 2b~~) and HO-1 (~~Fig. 3e~~), and these effects were abolished by either α -RAGE IgC (~~Fig. 2b and e~~) or sRAGE, supporting the concept that RAGE-dependent $A\beta$ BBB transport initiates cellular stress in brain. RAGE-dependent $A\beta$ -induced cellular stress was found either after cerebral arterial or systemic intravenous administration of $A\beta$, and persisted in brain for few hours. ~~Fig. 2d illustrates expression~~ Expression of TNF- α , IL-6 and HO-1 was observed in brain 2 hrs after i.v. administration of $A\beta_{1-40}$ at low nanomolar level.

Please replace the paragraph beginning on page 32, line 32, with the following paragraph:

Systemic administration of $A\beta_{1-40}$ (either human or murine) at low nanomolar concentrations resulted in time-dependent decrease in the CB, but did not affect systemic arterial blood pressure (~~Fig. 3a~~). Reductions in the CBF were detectable after 20-30 min of $A\beta$ administration, and maximal decrease in the CBR was observed between 40-60 min. CBF changes were completely antagonized by circulating α -RAGE at 40 μ g/ml (~~Fig.~~

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3b). A β -induced cerebral vasospasm was antagonized by α -RAGE in a dose-dependent manner, was abolished by sRAGE, but was not affected by an irrelevant antibody (~~Fig. 3e~~).

Please replace the paragraph beginning on page 33, line 13, with the following paragraph:

~~Fig. 4a shows significant~~ A significant decrease in basal CBF values was observed in 9 months old Tg APPsw+/- mice compared to age-matched control mice as determined by laser Doppler flowmetry, and confirmed by quantitative autoradiographic analysis. There was no difference in the arterial blood pressure between wild type and TG APPsw+/- mice (~~Fig. 4a~~). Infusion of α -RAGE dramatically increased the CBF in Tg APPsw+/- mice (~~Fig. 4b~~), and the effect was maximal between 60-120 min after systemic administration of α -RAGE. An irrelevant IgC did not affect the CBF in Tg APPsw+/- mice, as indicated by moderate reduction in expression of TNF- α , IL-6 and HO-1 (~~Fig. 4c~~). Expression of RAGE on brain microvessels was enhanced in Tg APPsw+/- mice (~~Fig. 4d left~~), and increased vascular expression of RAGE was associated with accumulation of A β in AD brains (~~Fig. 4d right~~).